## REMARKS/ARGUMENTS

### I. Status of Claims and Formal Matters

Claims 1-13 and 15-26 are pending in this application. Claims 8-12, 20 and 21 have been withdrawn from consideration. Claim 14 was previously cancelled. Claim 6 is herein canceled. Claims 1, 13, 23, 24, 25 and 26 are proposed to be amended. Upon entry of the proposed amendments, claims 1-5, 7-13 and 15-26 are pending with claims 1-5, 7,13, 15-19 and 22-26 under active consideration. Applicant respectfully requests entry of the proposed amendments.

Claim 1 is amended to specify that the fusion protein is "soluble" and that when the protein fragment or peptide is derived from GAD, it comprises GAD1 or GAD2. Support for this amendment may be found in the specification as filed, at least at page 8 lines 12 – 14 and 13, lines 4-5. Claims 13, 25 and 26 are amended to provide antecedent basis. Claims 23 and 24 are amended to remove the word "in". Accordingly, no new matter is added by the proposed amendments.

### II. Patentability Arguments

#### A. Objection to the Abstract and Title

The Abstract and Title stand objected to because, according to the Examiner, they do not adequately describe the claimed invention. While recognizing that multiple embodiments and inventions are disclosed in the instant specification and in no way acknowledging agreement with this rejection, Applicants herein amend the title and abstract of the specification for reasons unrelated to patentability and solely to expedite prosecution of the instant Application. Accordingly, Applicants respectfully request that the objections to the Abstract and Title be withdrawn.

#### B. Claim Rejections

1) **The Rejections Under 35 U.S.C. § 112, First Paragraph, For Lack of Written Description Should Be Withdrawn**

Claims 1-7, 13, 15-19 and 22-24 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, according to the Examiner, "[t]here is insufficient written description to show that Applicant was in possession of a 'protein fragment or peptide derived from GAD', except for GAD65 peptides 524-543 and 206-220. Applicants respectfully traverse this rejection in view of the amendments proposed herein.

Applicant herein amends claim 1 to recite that where the protein fragment or peptide is derived from GAD, it comprises GAD1 or GAD2, for which the Examiner has acknowledged sufficient written description. Accordingly, Applicants respectfully request the withdrawal of the rejections of claims 1-7, 13, 15-19 and 22-24 under 35 U.S.C. § 112, first paragraph.

**2) <u>The Rejections Under 35 U.S.C. § 112, First Paragraph, For Lack of Enablement Should Be Withdrawn</u>**

Claims 1-7, 13, 15-19 and 22-26 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner alleges that "the specification provides insufficient evidence that the claimed method could effectively function as a method for suspending, preventing or delaying the onset of type I diabetes." OA at 3. Applicants respectfully traverse this rejection.

As an initial matter, Applicants respectfully point out that when an examiner concludes that an application is describing an invention that is non-useful, inoperative, or contradicts known scientific principles, whether under 35 U.S.C. §§ 112 or 101, the ***burden is on the examiner*** (not on the Applicant) to provide a reasonable basis to support this conclusion. MPEP 2164.07I.B. Only after the examiner has provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provde rebuttal evidence sufficient to convince one of ordinary skill in the art of the invention's asserted utility. *Id.*

Moreover, it is well settled that a specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as

being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

As is discussed in detail below, Applicants respectfully submit that the Examiner has not provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility and has thus not established a *prima facie* case of lack of utility/operability under 35 U.S.C. § 112, first paragraph. Further, even if such *prima facie* case has been established, which is not admitted, Applicants provide herewith rebuttal evidence in the form of a Declaration of co-inventor Dr. Habib Zaghouani.

**i. No *Prima Facie* Case of Lack of Enablement has been Established.**

The Examiner relies on three references for the proposition that peptides (whether APLs or not) that work in *in vivo* small animal disease models cannot be expected to work in humans. Specifically, the Examiner relies on (1) Marketletter (9/13/99), as allegedly "teach[ing] the complete failure in human trials of two peptides designed for tolerance induction"; (2) Anderton (2001), as allegedly demonstrating that altered peptide ligands (APLs) are "even more unpredictable" and "can be dangerous...due to adverse reactions"; and (3) Dong *et al.* (1999) as disclosing that "translating these [tolerance] studies into larger animals and humans has been much more difficult to achieve." Insofar as the Examiner's rejections are based on APLs, the rejections are moot due to the amendments to claim 1. With respect to Marketletter and Dong *et al.*, Applicants respectfully submit that the Examiner's analysis fails to demonstrate a *prima facie* case that the present claims are not enabled. For at least the reasons discussed below, the three references relied on by the Examiner simply cannot lead to a conclusion that the instant specification "provides insufficient evidence that the claimed method could effectively function as a method for suspending, preventing or delaying the onset of type I diabetes (IDDM)" as asserted in the Office Action at page 3.

Marketletter describes clinical trials of two peptides, Myloral (for multiple sclerosis, MS) and Colloral (for rheumatoid arthritis, RA). MS and RA, while both autoimmune diseases, display a very different pathophysiology than type 1 diabetes and the animal models for these diseases are quite different from the non-obese diabetic (NOD) mouse model employed in the

instant specification and examples. Moreover, Myloral and Colloral are each free peptides. In contrast, the instant invention employs a fusion protein comprising at least one immunoglobulin having a diabetogenic peptide/fragment inserted within the variable region which "increase[s] presentation to T cells by 100-fold relative to free peptide." *See* specification, page 2, line 25 bridging to page 3, line 1. In fact, the Examiner has not established any nexus whatsoever between the clinical trials cited in Marketletter and the NOD model or the instant invention, aside from a vague and unfounded assertion that simply because the clinical studies in Marketletter were unsuccessful that the current claims are nonenabled.[1] Dong *et al.*, which reviews transplantation tolerance, defined as "the absence of a destructive immune response against the graft in an immunocompetent host," is even further attenuated from the instant invention.

Any lack of success in the Marketletter trials could have been due to any number of variables including inadequate study design. For example, choices to expedite the testing process predicated on AutoImmune's financial situation may have contributed to the outcome – early dosing trials were all but omitted which may have resulted in dosages being too low. Indeed, Baxter and Duckworth, Drug Discovery Today: Disease Models, Vol. 1, Issue 4, Dec. 2004, 451-455, submitted herewith, warn that "[r]ecent skepticism over failed clinical trials of candidate therapies identified in the mice is probably unwarranted, because, generally speaking, the trial protocols concerned did not compensate for limitations in clinical translation, such as dose escalation and narrow therapeutic windows, that were clearly identified by the preclinical studies." *See* Baxter and Duckworth, page 453, top of column 1.

The NOD mouse strain used in the present application, as noted by Baxter and Duckworth at page 452, "is the most characterized and best-validated model of autoimmune diabetes; it is the **gold standard** for modeling aetiological, immunological, pathological and genetic aspects of the disease" (emphasis added). According to MPEP § 2164.02, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. The

[1] Contrary to the Examiner's assertion, neither the Myloral nor the Colloral clinical study was a "complete failure" – in fact, neither Myloral nor Colloral were ineffective treatments; rather, their tests simply proved them to be no more efficacious than placebos. The placebo effect in these trials was greater than others previously recorded.

Examiner has not presented any evidence that data obtained using the NOD mouse is not predictive of therapeutic results in patients with type 1 diabetes; on the contrary, as noted *supra*, the NOD mouse is the "gold standard" animal model for type 1 diabetes. A rigorous or invariably exact correlation is not required nor is there any decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders. If reasonably correlated to the particular therapeutic or pharmacological utility, data generated from testing in an animal model almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. See MPEP § 2107.03. Such certainly must be the case for data generated using the "gold standard" animal model.

For at least the foregoing reasons, Applicants submit that no *prima facie* case of lack of enablement has been established. Withdrawal of this rejection is respectfully requested.

**ii. Rebuttal of Alleged *Prima Facie* Case of Lack of Enablement**

Even if a *prima facie* case of lack of enablement has been established, which is not admitted, Applicants submit herewith a signed declaration from Habib Zaghouani, a named inventor of the instant application, demonstrating that administration of Ig-GAD2 to pre-diabetic NOD mice prevents the onset of type 1 diabetes. This evidence demonstrates that the disclosure as filed would have enabled the clamed invention for one skilled in the art at the time of filing.

In view of the foregoing arguments and evidence, Applicants respectfully submit that the rejections of claims under 35 U.S.C. § 112, first paragraph, for lack of enablement are improper and/or have been overcome and respectfully request withdrawal of the same.

3) The Rejections Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-7, 13, 15-19 and 22-26 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 98/30706 in view of Kaufman *et al.* (1992). According to the Examiner, WO 98/30706 teaches the treatment of autoimmune disorders, including IDDM employing an engineered fusion protein but fails to teach the use of GAD65 as the autoantigen. Kaufman *et al.* teach that GAD65 is a well known IDDM autoantigen. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the Examiner must provide a clear articulation of the reasons why the claimed invention would have been obvious. Second, there must be a reasonable expectation of success. That is, the hypothetical person of ordinary skill in the art, at the time the invention was made, must have had a reasonable expectation that the proposed modification or combination would work to produce beneficial results. Finally, the references when combined must teach or suggest all the claim limitations. *See* MPEP § 2143. The burden of establishing a *prima facie* case of obviousness lies with the Examiner, and the expectation of success must be found in the prior art, not the applicant's disclosure." *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir. 1988).

As is discussed in detail below, Applicants respectfully submit that the Examiner has failed to provide a rationale for why one of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention at the time the instant application was filed. While obviousness does not require absolute predictability, at least some degree of predictability is required. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). In the present case, the outcome lacked any predictability whatsoever. For at least this reason, Applicants submit that no *prima facie* case of obviousness has been established.

Biological and chemical processes are unpredictable; this unpredictability is expressly recognized by the Examiner at pages 5-6 of the Office Action in which the Examiner states that, especially in view of Legge *et al.* (1998), "it is just as likely that the method of the instant claims would actually exacerbate disease as treat or prevent it." The fact that at the time the present application was filed it was equally likely that the presently claimed embodiments of the invention would exacerbate disease as treat or prevent it is *per se* unpredictability. On this basis alone Applicants submit that the second prong required for a *prima facie* case of obviousness has not been established.

WO 98/30706 casts further uncertainty. WO 98/30706 discloses that PLP1 peptide, encompassing encephalitogenic sequence corresponding to amino acid residues 139-151 of naturally occurring proteolipid protein, acts as an *agonist* and induces encephalitogenic T cells. In contrast, replacing 144W and 147H with 144L and 147 R, respectively, within PLP1 generates an *antagonist* peptide analog, PLP-LR, that interferes with TCR triggering by PLP1 and inhibits T cell activation. WO 98/30706 teaches that Ig-PLP1, when injected into mice, induces a strong

specific T cell response to the PLP1 peptide. This T cell response is attenuated when Ig-PLP-LR is co-administered to the mice, which the authors attribute to the induction of a relatively high proliferative response to PLP-LR and practically no response to PLP1. However, WO 98/30706 teaches that administration of Ig-PLP-LR alone actually induced T cells which cross-reacted with both PLP1 and PLP-LR peptides: "antigen specific T cells induced either by IG-PLP1 or by IG-PLP-LR were refractory to down-regulation by peptide mixtures and proliferated significantly when they were in vitro stimulated simultaneously with both PLP1 and PLP-LR." *See* WO 98/30706, page 34, lines 9-12. Thus, WO 98/30706 teaches that in order to observe any reduction in T cell response against an encephalitogenic antigen, Ig-PLP1 and Ig-PLP-LR must be co-administered. In contrast, as noted *supra*, PLP-LR peptide, administered on its own, interferes with TCR triggering by PLP1 and inhibits T-cell activation. Accordingly, one of ordinary skill in the art at the time the present application was filed lacked any reasonable expectation of success in achieving the instantly claimed invention by combining the teachings of WO 98/30706 with Kaufman *et al.*

In view of the foregoing, Applicants respectfully submit that the cited references, alone or in combination, fail to establish a *prima facie* case of obviousness. At the very least, no reasonable expectation existed that the proposed modification or combination would work to produce beneficial results. Accordingly, Applicants respectfully request that the Examiner withdraw the rejections of claims 1-7, 13, 15-19 and 22-26 under 35 U.S.C. § 103(a).

4) The Rejections Under 35 U.S.C. § 112, First Paragraph, For New Matter Should Be Withdrawn

Claims 1-7, 13, 15-19 and 22-26 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly containing new matter. Specifically, the Examiner states that he cannot find support for the phrase "at least one CDR" and the phrase "at least one protein fragment or peptide derived from GAD." Applicants respectfully traverse this rejection in view of the presently proposed amendments.

With regard to the Examiner's rejection of the phrase "at least one CDR," in order to expedite the allowance of the instant Application and without in any way acknowledging agreement with the Examiner's statement with respect to the presence of new matter in the

claims of the instant Application, Applicants herein amend claim 1 to specify that the protein fragment or peptide derived from GAD comprises GAD1 or GAD2 and to replace the phrase "composed of at least one CDR" with the phrase "comprising a CDR1, a CDR2, or a CDR3." Support for the amendment may be found at least in claim 6 of the specification as filed and page 22, lines 3-5. Accordingly, the rejections of claims 1-7, 13, 15-19 and 22-26 under 35 U.S.C. § 112, first paragraph, for allegedly containing new matter is moot and Applicants respectfully request withdrawal of the rejections.

5) The Rejections For Obviousness-type Double Patenting Should Be Withdrawn

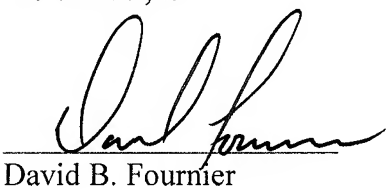
Claims 1-7, 13, 15-19 and 22-26 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over: (1) claims 62-65 of U.S. Patent Application No. 10/510, 411; (2) claims 1-7 and 13-16 of U.S. Patent Application No. 11/290,070; and (3) claims 1-7 and 13-16 of U.S. Patent Application No. 11/425,084. Applicants wish to defer the response to these provisional rejections until the claims are otherwise allowable.

## CONCLUSION.

Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is hereby respectfully invited to contact the undersigned attorney at the number listed below.

Respectfully submitted,

HOWREY, LLP



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**Attachments**

1. Baxter and Duckworth, Drug Discovery Today: Disease Models, Vol. 1, Issue 4, Dec. 2004, 451-455
2. Declaration of Habib Zaghouani